METHODS FOR STABLY INCORPORATING SUBSTANCES WITHIN DRY FOAMED GLASS MATRICES AND COMPOSITIONS OBTAINED THEREBY (FGMs)

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PENDING CLAIMS AS AMENDED BY MAY 2, 2000 RESPONSE

1. (Four Times Amended) A method for producing foamed glass matrices (FGMs) containing a biologically active agent, comprising the steps of:

(a) preparing an initial mixture comprising at least one glass matrix-forming material containing a biologically active agent selected from the group consisting of a therapeutic agent, a prophylactic agent, a pharmaceutically effective substance and a diagnostic reagent, and solvent(s) for the glass matrix-forming material;

(b) evaporating a portion of the solvent(s) from the mixture to obtain a syrup;

(c) boiling the syrup under less than atmospheric pressure to produce foaming of the syrup; and

(d) continuing step (c) until the boiling results in the formation of a solid foam and produces a foamed glass matrix containing the biologically active agent.

2. The method according to claim 1, wherein the glass matrix-forming material is a stabilizing polyol.

3. The method according to claim 2, wherein the stabilizing polyol is a carbohydrate.

4. The method according to claim 3, wherein the carbohydrate is natural or synthetic.

5. (Amended) The method according to claim 3, wherein the carbohydrate is a chemically or enzymatically modified carbohydrate.

6. (Amended) The method according to claim 3, wherein the carbohydrate is selected from the group consisting of glucose, maltulose, iso-maltulose, lactulose, sucrose, maltose, lactose, isomaltose, raffinose, stachyose, melezitose, dextran, fructose, galactose, mannose, cellibiose, mannobiose, and sugar alcohols obtained by reduction of disaccharides.

7. The method according to claim 3, wherein the carbohydrate is trehalose.

8. (Amended) The method according to claim 1, wherein the solvent comprised in the initial mixture is aqueous.

9. (Amended) The method according to claim 8, wherein the solvent comprised in the initial mixture is an aqueous buffer. - Buffer - AA

10. (Amended) The method according to claim 1, wherein the solvent comprised in the initial mixture is organic.

12. (Amended) The method according to claim 1, wherein the solvent comprised in the initial mixture is a combination of aqueous and organic liquids.

13. (Amended) The method according to claim 8, wherein the solvent is present in the initial mixture in an amount of about 5% to 95% by volume. - 6% Dextran 5% Glucose } 1.5 mols = .15g CaHO / 0.025 H_2O = 12% H_2O

15. (Amended) The method according to claim 1, wherein the evaporation in step (b) occurs at an external temperature of about 0°C to 90°C.

16. (Amended) The method according to claim 1, wherein the evaporation in step (b) occurs at an external temperature of about 15°C to 60°C.

17. (Twice Amended) The method according to claim 1, wherein the evaporation in step (b) occurs at an external temperature of about 25°C (RT) to 45°C. - new matter ?

18. (Amended) The method according to claim 1, wherein the evaporation in step (b) results in removal of 5-95% of the solvent.

19. (Twice Amended) The method according to claim 1, wherein the evaporation during step (b) occurs at less than atmospheric pressure.

20. (Amended) The method according to claim 19, wherein the external pressure during step (b) is about 0.1 to 30 mm Hg.

21. (Amended) The method according to claim 19, wherein the external pressure during step (b) is about 1 to 20 mm Hg.

22. (Amended) The method according to claim 19, wherein the external pressure during step (b) is about 7.5 to 12.5 mm Hg.

23. (Amended) The method according to claim 19, wherein the external pressure during step (b) is about 10 mm Hg.

26. (Thrice Amended) The method according to claim 1, wherein the pressure during step (c) is below 30 mm Hg.

27. (Amended) The method according to claim 1, wherein the pressure during step (c) is about 0.01 to 10 mm Hg.

28. (Amended) The method according to claim 1, wherein the pressure during step (c) is about 0.01 to 0.5 mm Hg.

29. (Amended) The method according to claim 1, wherein the pressure during step (c) is about 0.05 mm Hg.

30. (Thrice Amended) The method according to claim 1, wherein the foaming during step (c) occurs at a temperature above 25°C.

31. The method according to claim 1, wherein the temperature during step (c) is about 0°C to 80°C.

32. The method according to claim 1, wherein the temperature during step (c) is about 10°C to 60°C.

33. The method according to claim 1, wherein the temperature during step (c) is about 15°C to 45°C.

34. The method according to claim 1, wherein the FGM has a residual moisture content of about 0.1 to 12% (w/w).

35. The method according to claim 34, wherein the FGM has a residual moisture content of about 1 to 5% (w/w).

36. (Amended) The method according to claim 1, further comprising the step of adding at least one additive to the mixture before step (c).

37. The method according to claim 36, wherein the additive is at least one volatile salt.

38. The method according to claim 37, wherein the volatile salt is selected from the group consisting of ammonium acetate, ammonium bicarbonate, and ammonium carbonate.

39. The method according to claim 37, wherein the volatile salt is present in an amount from about 0.01 to 5 M.

40. (Twice Amended) The method according to claim 36, wherein the additive is at least one salt that decomposes under less than atmospheric pressure to give a gaseous product.

41. The method according to claim 40, wherein the decomposing salt is selected from the group consisting of sodium bicarbonate and sodium metabisulphite.

42. (Amended) The method according to claim 36, wherein the additive is at least one volatile organic liquid.

44. The method according to claim 36, wherein the additive is a foam stabilizing agent.

45. The method according to claim 44, wherein the foam stabilizing agent is a viscosity modifier.

46. The method according to claim 45, wherein the viscosity modifier is a guar gum.

47. (Amended) The method according to claim 44, wherein the foam stabilizing agent is a surface-active amphipathic molecule.

48. The method according to claim 36, wherein the additive is an inhibitor of the Maillard reaction.

54. (Twice Amended) The method according to claim 62, wherein the biologically active agent to be preserved is selected from the group consisting of cells, subcellular components, bacteria, and viruses.

55. (Twice Amended) The method according to claim 62, wherein the biologically active agent to be preserved is selected from the group consisting of lipids, proteins, peptides, peptide mimetics, oligosaccharides, oligonucleotides, and protein nucleic acid hybrids.

56. (Twice Amended) The method according to claim 55, wherein the biologically active agent to be preserved is a protein or peptide selected from the group consisting of enzymes, monoclonal antibodies, interferons, interleukins, cytokines, hormones, and other growth factors.

57. (Thrice Amended) The method according to claim 62, wherein the biologically active agent to be preserved is a vaccine.

58. (Amended) The method according to claim 57, wherein the vaccine comprises a component selected from the group consisting of live and attenuated viruses, nucleotide vectors encoding antigens, live and attenuated bacteria, antigens, antigens mixed with adjuvants, and haptens coupled to carriers.

59. (Twice Amended) A method for providing a reconstituted biologically active agent, comprising producing an FGM according to the method of claim 1 into which the biologically active agent is incorporated, and then contacting the FGM with sufficient solvent for the glass matrix forming material to dissolve the material.

61. (Twice Amended) The method according to claim 59, wherein the solvent with which the FGM is contacted is an aqueous buffer.

62. (Four Times Amended) A method for preserving a biologically active agent within a foamed glass matrix (FGM) comprising the steps of:

(a) preparing an initial mixture comprising at least one glass matrix-forming material containing a biologically active agent to be preserved selected from the group consisting of a therapeutic agent, a prophylactic agent, a pharmaceutically effective substance and a diagnostic reagent and solvent(s) for the glass matrix-forming material;

(b) evaporating a portion of the solvents from the mixture to obtain a syrup;

(c) boiling the syrup under less than atmospheric pressure to produce foaming of the syrup; and

(d) continuing step (c) until the boiling results in the formation of a solid foam and produces a foamed glass matrix containing the biologically active agent.

63. (Twice Amended) The method according to claim 62, wherein the solvent is a solvent for both the glass matrix-forming material and the biologically active agent.

64. (Four Times Amended) The method according to claim 62, wherein the mixture prepared in step (a) comprises different solvents selected from the group consisting of aqeuous, organic or a mixture of both, for the glass matrix-forming material and the biologically active agent.

65. (Amended four times) A method for producing a single dose of a biologically active agent, comprising the steps of:

(a) preparing an initial mixture comprising at least one glass matrix-forming material containing a biologically active agent to be preserved selected from the group consisting of a therapeutic agent, a prophylactic agent, a pharmaceutically effective substance and a diagnostic reagent and solvent(s) for the glass matrix-forming material;

(b) evaporating a portion of the solvent(s) from the mixture to obtain a syrup;

(c) boiling the syrup under less than atmospheric pressure to produce foaming of the syrup; and

(d) continuing step (c) until the boiling results in the formation of a solid foam and produces a foamed glass matrix containing the biologically active agent.

66. (Twice Amended) The method according to claim 65, wherein the solvent is a solvent for both the glass matrix-forming material and the biologically active agent.

67. (Four Times Amended) The method according to claim 65, wherein the mixture prepared in step (a) comprises different solvents selected from the group consisting of aqeuous, organic or a mixture of both, for the glass matrix-forming material and the biologically active agent.

69. (Amended) The method according to claim 65, further comprising contacting the FGM with sufficient solvent for the glass matrix forming material to dissolve the material.

71. (Four Times Amended) A foamed glass matrix (FGM) containing a biologically active agent obtained by the method of claim 1.

72. (Thrice Amended) A composition comprising at least one biologically active agent preserved in an FGM, obtained by the method of claim 62, wherein step (c) is conducted at less than atmospheric pressure.

78. (Amended) The method according to claim 1, further comprising reducing residual moisture from the FGM formed in step (d).

79. (Amended) The method according to claim 1, wherein the syrup has a viscosity of 10^6-10^7 Pascal seconds.

80. (Amended) The method according to claim 3, wherein the carbohydrate is selected from the group consisting of trehalose, maltitol, lactitol, palatinit, α-D-glucopyranosyl-1→6-sorbitol, and α-D-glucopyranosyl-1→6-mannitol.

81. (Twice Amended) The method according to claim 62, wherein the biologically active agent to be preserved is a physiologically active molecule selected from the group consisting of Cyclosporin A and other immunosuppressive agents, beta blockers, H2 agonists, H2 antagonists, steroids, sex hormones, Phenobarbitals, analgesics, antimicrobials, antivirals, antiinflammatories, antiarthritics, antispasmodics, antidepressants, antipsychotics, tranquilizers, antianxiety drugs, narcotics, antiparkinsonism agents, cholinergic agonists, chemotherapeutics, appetite suppressants, anticholinergics, antiemetics, antihistaminics, antimigraine agents, vasodilators, contraceptives, antithrombotic agents, diuretics, antihypertensives, cardiovascular drugs, and opioids.

82. The method according to claim 58, wherein the component is Hepatitis B Surface Antigen, measles virus, or oral polio virus.

83. (Twice Amended) The method according to claim 62, further comprising reducing residual moisture from the FGM formed in step (d).

84. (Amended) The method according to claim 62, wherein the biologically active agent to be preserved is in suspension in the mixture.

85. (Amended) The method according to claim 62, wherein the biologically active agent to be preserved is dissolved in the mixture.

86. (Amended) The composition of claim 72, wherein the biologically active agent is selected from the group consisting of cells, subcellular components, bacteria, and viruses.

87. (Twice Amended) The composition of claim 72, wherein the biologically active agent is selected from the group consisting of lipids, proteins, peptides, peptide mimetics, oligosaccharides, oligonucleotides, protein nucleic acid hybrids, and physiologically active molecules.

88. (Amended) The composition of claim 72, wherein the biologically active agent is a protein or peptide selected from the group consisting of enzymes, monoclonal antibodies, interferons, interleukins, cytokines, hormones, and other growth factors.

89. (Amended) The composition of claim 72, wherein the biologically active agent is a vaccine comprising a component selected from the group consisting of live and attenuated viruses, nucleotide vectors encoding antigens, live and attenuated bacteria, antigens, antigens mixed with adjuvants, and haptens coupled to carriers.

90. The composition of claim 72, having a residual moisture content of about 0.1 to 5% (w/w).

91. (Thrice Amended) A method for producing foamed glass matrices (FGMs) containing a biologically active agent, comprising the steps of:

(a) preparing an initial mixture comprising at least one glass matrix-forming carbohydrate, the biologically active agent selected from the group consisting of a therapeutic agent, a prophylactic agent, a pharmaceutically effective substance and a diagnostic reagent, solvents for the carbohydrate and biologically active agent and at least one foam-promoting

additive which is a volatile salt or a salt that decomposes at less than atmospheric pressure to give a gaseous product;

(b) evaporating a proportion of the solvent from the mixture to obtain a syrup;

(c) boiling the syrup under less than atmospheric pressure to produce foaming of the syrup; and

(d) continuing step (c) until the boiling results in the formation of a solid foam and produces a foamed glass matrix containing the biologically active agent.

92. (New) The method of claim 91, wherein the carbohydrate is trehalose, lactitol or palatinit.

93. (Amended) An FGM incorporating a biologically active agent to be preserved, formed according to the method of claim 91.

94. (Four Times Amended) A method for producing foamed glass matrices (FGMs) containing a biologically active agent, comprising the steps of:

(a) preparing an initial mixture comprising at least one glass matrix-forming carbohydrate, carbohydrate alcohol or carbohydrate derivative, the biologically active agent, a pharmaceutically effective substance and a diagnostic reagent, an aqueous solvent therefor, and a foam-promoting additive which is a volatile organic solvent;

(b) evaporating a portion of the aqueous and organic solvents from the mixture to obtain a syrup;

(c) boiling the syrup under less than atmospheric pressure to produce foaming of the syrup; and

(d) continuing step (c) until the boiling results in the formation of a solid foam and produces a foamed glass matrix containing the biologically active agent.

95. The method of claim 94, wherein the carbohydrate is trehalose, lactitol or palatinit.

96. (Amended) An FGM incorporating a biologically active agent to be preserved, formed according to the method of claim 94.

97. (Amended) The method according to claim 65, which further comprises the reducing of the residual moisture from the product of step (d).

98. A method for dissolving a foamed glass matrix which incorporates a biologically active agent selected from the group consisting of a therapeutic agent, a prophylactic agent, a pharmaceutically effective substance and a diagnostic reagent comprising contacting the foamed glass matrix with sufficient solvent(s) to dissolve the foamed glass matrix.